PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Jack STAPLETON *et al.*

Serial No.: 09/954,975

Filed: September 18, 2001

For: METHODS FOR TREATING HUMAN IMMUNODEFICIENCY VIRUS INFECTIONS WITH GALLIUM COMPOSITIONS

Group Art Unit: 1616

Examiner: F. Choi

Atty. Dkt. No.: IOWA:033US/SLH

REPLY BRIEF

CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Mail Stop Appeal Brief – Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date below:

July 19, 2004
Date

Steven L. Highlander

TABLE OF CONTENTS

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Jack STAPLETON *et al.*	Group Art Unit: 1616
Serial No.: 09/954,975	Examiner: F. Choi
Filed: September 18, 2001	Atty. Dkt. No.: IOWA:033US/SLH
For: METHODS FOR TREATING HUMAN IMMUNODEFICIENCY VIRUS INFECTIONS WITH GALLIUM COMPOSITIONS	

REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellant hereby submits an original and two copies of this Reply Brief to the Board of Patent Appeals and Interferences in response to the Examiner's Answer, mailed May 17, 2004. Thus, this reply is due on July 17, 2004. No fee is believed due; however, should any fees be due, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account No. 50-1212/IOWA:033US/SLH. Please date stamp and return the enclosed postcard to evidence receipt of this document.

I. Real Party in Interest

The real party in interest remains the assignee, University of Iowa Research Foundation, Iowa City, IA.

II. Related Appeals and Interferences

There are no interferences or appeals for related cases.

III. Status of the Claims

Claims 1-40 were filed with the original application. Claims 1-10 have been canceled. Claims 11-40 stand rejected. A copy of the rejected claims is attached as APPENDIX 1 to this brief.

IV. Summary of the Invention

In accordance with the present invention, there is provided a method of treating a human subject infected with human immunodeficiency virus (HIV) comprising administering to said subject an amount of a gallium composition effective to inhibit HIV replication. HIV may be HIV-1 or HIV-2. The gallium composition may be gallium nitrate, or may be a gallium-hydroxypyrone complex. The effective amount can be described as: achieving *in vivo* concentrations of about 1 to about 30 μM, or more specifically about 3 to about 20 μM. Alternatively, the effective amount is about 750 mg/m^2 given every two to three weeks, or about 100 to about 300 mg/m^2 per day. In one embodiment, the gallium composition is provided at levels sufficient to provide a blood plasma gallium concentration of 0.1 to 5.0 μg/ml. The gallium composition may be administered orally, for example, in the form of a tablet or a capsule. Alternatively, the gallium composition is administered intravenously. Specification at page 4, line 25 to page 5, line 7.

In yet another embodiment, the method further comprises treating the subject with a second anti-viral agent in addition to the gallium composition, for example, a nucleoside analog that inhibits reverse transcriptase (NRTIs). Nucleoside analogs include dideoxyinosine,

dideoxycytidine and 5-azidothymidine. Other anti-viral agents include protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Specification at page 5, lines 8-12.

In still yet another embodiment, there is provided a method of reducing virus shed from a human subject infected with HIV comprising administering to said subject an amount of a gallium composition effective to inhibit HIV replication. The method may also provide for reduced virus burden in a human subject infected with HIV, inhibition of loss of T cells in a human subject infected with HIV, increase in T cell numbers, in a human subject infected with HIV, or inhibition of development of acquired immunodeficiency syndrome in a human subject infected with HIV. Specification at page 5, lines 13-19.

In still a further embodiment, there is provided a therapeutic composition comprising (a) a gallium composition; and (b) a nucleoside inhibitor. The gallium composition may be gallium nitrate, or may be a gallium-hydroxypyrone complex. The NTRI may be one or more of the compounds selected from the group of didexoyinosine, dideoxycytidine and 5-azidothymidine. Also provided is a kit comprising, in suitable container means (a) a gallium composition; and (b) a nucleoside reverse transcriptase inhibitor. Specification at page 5, lines 20-26.

V. Issues on Appeal

Are claims 11-13 and 16-40 obvious over U.S. Patent 5,093,134 ("the '134 patent"; Exhibit A) and Narasimhan *et al.* ("Narasimhan"; Exhibit B)?

Are claims 11-40 obvious over Narasimhan, U.S. Patent 5,525,598 ("the '598 patent"; Exhibit C) and U.S. Patent 5,883,088 ("the '088 patent"; Exhibit D)?

VI. Grouping of the Claims

The claims do not stand and fall together, as discussed in §IX.C, below.

VII. Summary of the Argument

The present rejections, though using different combinations of references, are both based on the same flawed premise – that the knowledge of gallium inhibition of ribonucleotide reductase, can render its use as an HIV therapeutic obvious. The secondary references, some of which teach the inclusion of gallium in the context of more complex compositions, certainly do not render the use of gallium *per se* obvious since ***none of them teach or suggest that there would be any therapeutic benefit in treating HIV-infected patients with gallium***. In sum, the rejection is based on a hindsight reconstruction of the invention, using appellants' disclosure as a road map. At best, the art presents an obvious to try scenario would ***not*** be the proper basis for rejection.

VIII. Summary of Examiner's Answer

First, the examiner argues that, in general, motivation to modify the prior art or combine it with additional references need not be found expressly in the art, but may be implied or reasoned from knowledge available to those of ordinary skill in the art.

Second, the examiner argues that since gallium is known to inhibit ribonucleotide reductase and reverse transcriptase, the failure of the abstract to mention anti-viral applications or HIV is of no significance. Rather, since both of these enzymes are known to be targets for the treatment of HIV, the examiner finds nothing more to be need. Further, the use of gallium-containing compounds by Murrer *et al.* is said to further create motivation. The examiner maintains that appellants are improperly attacking the references individually, and that the rejection has adequately addressed the issue of likelihood of success.

Third, the examiner again defends the prior art as teaching that gallium compositions inhibit viral enzymes, and that they thus would be obvious choices to treat HIV. The examiner

dismisses the inferiority of gallium-containing compounds, citing case law that allegedly supports a holding of obviousness against less active substances. Again, the examiner attacks applicants' reasoning as based on the references individually, and not on their combined teachings.

And fourth, the examiner denies any separate patentability for claims drawn to reducing virus shed, reducing viral burden, and inhibiting development of AIDS. The examiner argues that since the step of providing a gallium composition is common to each claim, they are obvious for the same reasons given above.

IX. Reply

A. Attacking References Individually

The examiner has argued, with respect to both §103 rejections, that appellants are improperly attacking the references individually. However, as pointed out in their Appeal Brief, appellants are arguing, in one aspect, that the references would not be combined as suggested by the examiner. In order to do so, ***it is impossible not to discuss the references individually***. Thus, the examiner's continued citation of legal truisms, without recognition of the facts or arguments presented here, does not advance the PTO's position.

As discussed before, it is not disputed that Narasimhan discloses that gallium inhibits ribonucleotide reductase, or that gallium nitrate has been shown to inhibit reverse transcriptase as early as 1974. However, that reference is silent on HIV therapies. So, the question is why one would combine Narasimhan with the '134 patent, because the motivation does ***not*** exist in the former.

Admittedly, the '134 patent addresses HIV therapies. But the key issue is that the ***only explicit mention*** of gallium in the entire '134 patent is at col. 3, where gallium is listed as one of

ten possible metal ions, and in Table (columns 3-4), where two gallium-containing compounds were tested (out of 15 other compounds "according to the invention"). For the examiner to suggest that this minute disclosure, provided in this context, would provide sufficient motivation to combine these references is ***pure hindsight***. *In re Carroll*, 202 USPQ 571 (CCPA 1979) ("One of the more difficult aspects of resolving questions of non-obviousness is the necessity 'to guard against slipping into the use of hindsight.'"), citing *Graham v. John Deere Co.*, 148 USPQ 459 (U.S. Sup. Ct. 1965). Applicants submit that it is incumbent upon the examiner to find the suggestion to modify the primary reference ***in the prior art***, something which the examiner has failed to do here. *In re Soli*, 137 USPQ 797 (CCPA 1963). It is only after appellants have identified the activity of gallium against HIV that one is able to excise from the '134 the passing mention of that agent. Thus, it is the examiner, not appellants, who is engaging in an improper obviousness analysis under the controlling precedent. To reiterate, appellants respectfully submit that one of skill in the art, reading either document, would find no motivation to combine the two.

A similar argument stands against the combination of Narasimhan and the '598 and '088 patents. While one can clearly find in the '598 patent a connection between gallium and HIV, it is not a good one: "It has now been found that certain gallium (III) complexes have antitumor and antiviral activities. The invention gallium (III) complexes comprise gallium (III) complexes of N-heterocycles." Col. 1, lines 39-43. Far from focusing on gallium, the '598 patent discusses a complex heterocyclic compound that contains, as one aspect, gallium (III) ions. Moreover, there is only marginal information in the '598 patent on the activity of these compounds, and what information there is suggests that these compounds are far less effective at inhibiting HIV (low EC_{50}/IC_{50} ratio) than existing drugs such as AZT. Notably, the issued claims in the '598

patent ***are limited to use of these compounds to treating tumors***. Thus, the ***reasonable*** conclusion to be drawn from this disclosure is not that gallium itself can act as an antiviral, but even when it is part of a more complex compound, one would still doubt its efficacy even in that environment.

The examiner attempts to counter appellants' related "teaching away" argument by citation to *In re Gurley*, which indeed states that "a known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same purpose." In fact *Gurley* also states that "a reference will teach away if it suggests that the line of development flowing from the references's disclosure is unlikely to be productive of the result sought by the applicant" (citing *U.S. v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966). Once again, however, all legal truisms must applied to ***the facts*** of this case in order for their relevance to be establish.[1]

In *Gurley*, the question boiled down to whether the epoxy of the prior art could be employed in the creation of usable circuit boards. Clearly, the facts of that case lead to an affirmative answer. Here, however, the question is whether the gallium compounds of the present invention would be thought useable in light of the clear indication of reduced function in the '598 patent. The answer, again quite clear, is unequivocally in the negative.

In sum, the art of record had not been improperly examined piecemeal, but is has been properly evaluated for any reasonable basis of combination. Such basis is not evident. Further, the combination of this art based merely on the use of the word "gallium" ignores the true teachings of these references – that gallium itself has never shown any anti-viral activity by

[1] Please note the *Gurley* court's admonition that "such a rule cannot be adopted in the abstract, for it may not be applicable in all factual circumstance."

itself, and that it seems to diminish the activity of other compounds. Thus, there is no reasonable basis to posit the combination of these references, and the rejection remains improper.

B. Likelihood of Success

Perhaps the most troubling aspect of the instant rejections is the willingness of the PTO to gloss over the issue of likelihood of success. The PTO consistently takes the position, with respect to enablement of therapeutic patent applications – ***and with particular dogmatism regarding methods of treating HIV*** – that there must be evidence of operability of the claimed invention due to considerable unpredictability of the endeavor. Yet here, the examiner seems will to merely ***assume*** that the prior art amalgam will work without any concern for whether the prior art is, in fact, enabling. This is an inappropriate double-standard that flies in the face of PTO practice and procedure, as well as the established case law on likelihood of success. *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Precisely such a case is presented here.

The prior art does not provide sufficient information regarding the ability of gallium to act as a therapeutic agent against HIV. While the compounds of the '598 patent were shown to have marginal *in vitro* effects, these were not gallium *per se*, but compounds that contained gallium ***in the context of N-heterocycles***. As such, this reference says little, if anything, regarding the efficacy of gallium (or even gallium-containing N-heterocycles) to treat HIV. The '134 patent similarly obfuscates the issue of whether gallium in and of itself is therapeutic. Narasimhan is notably silent on treatments, and cannot therefore provide any meaningful comment on the issue of likelihood of success.

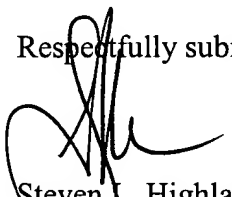
In light of these facts, the only reasonable conclusion is that the prior art provides, at best, an invitation to one of skill in the art to experiment with gallium as a therapeutic agent for HIV.

This is not, however, the standard for obviousness, and the rejection remains improper for yet this additional reason.

X. Conclusion

It is respectfully submitted, in light of the above, that all claims are non-obvious. Therefore, appellants request that the Board overturn each of the pending grounds for rejection.

Respectfully submitted,



Steven L. Highlander
Reg. No. 37,642
Attorney for Appellants

Fulbright & Jaworski
600 Congress Ave., Suite 2400
Austin TX 78701
512-536-3184

Date: July 19, 2004

APPENDIX 1 -- PENDING CLAIMS

11. A method of treating a human subject infected with human immunodeficiency virus (HIV) comprising administering to said subject an amount of a gallium composition effective to inhibit HIV replication.

12. The method of claim 11, wherein HIV is HIV-1.

13. The method of claim 11, wherein HIV is HIV-2.

14. The method of claim 11, wherein said gallium composition is gallium nitrate.

15. The method of claim 11, wherein said gallium composition is a gallium-hydroxypyrone complex.

16. The method of claim 11, wherein said effective amount achieves *in vivo* concentrations of about 1 to about 30 μM.

17. The method of claim 16, wherein said effective amount is about 3 to about 20 μM.

18. The method of claim 11, wherein said effective amount is about 750 mg/m^2 given every two to three weeks.

19. The method of claim 11, wherein said effective amount is about 100 to about 300 mg/m^2 per day.

20. The method of claim 11, wherein said effective amount is given in a unit dose of about 200 mg to about 1000 mg.

21. The method of claim 11, wherein said gallium composition is administered orally.

22. The method of claim 21, wherein said gallium composition is in the form of a tablet.

23. The method of claim 21, wherein said gallium composition is in the form of a capsule.

24. The method of claim 11, wherein said gallium composition is administered intravenously.

25. The method of claim 11, wherein said gallium composition is sufficient to provide a blood plasma gallium concentration of 0.1 to 5.0 μg/ml.

26. The method of claim 11, further comprising treating said subject with a second anti-viral agent.

27. The method of 26, wherein said second anti-viral agent is a nucleoside reverse transcriptase inhibitor (NRTI).

28. The method of claim 26, wherein said NRTI is didexoyinosine.

29. The method of claim 26, wherein said NRTI is dideoxycytidine.

30. The method of claim 26, wherein said NRTI is 5-azidothymidine.

31. A method of reducing virus shed from a human subject infected with human immunodeficiency virus (HIV) comprising administering to said subject an amount of a gallium composition effective to inhibit HIV replication.

32. A method of reducing virus burden in a human subject infected with human immunodeficiency virus (HIV) comprising administering to said subject an amount of a gallium composition effective to inhibit HIV replication.

33. A method of inhibiting loss of T cells in a human subject infected with human immunodeficiency virus (HIV) comprising administering to said subject an amount of a gallium composition effective to inhibit HIV replication.

34. The method of claim 33, wherein the number of T cells in said subject increases following treatment with said gallium composition.

35. A method of inhibiting development of acquired immunodeficiency syndrome in a human subject infected with human immunodeficiency virus (HIV) comprising administering to said subject an amount of a gallium composition effective to inhibit HIV replication.

36. A therapeutic composition comprising:

(a) a gallium composition; and

(b) a nucleoside inhibitor.

37. The composition of claim 36, wherein said gallium composition is gallium nitrate.

38. The composition of claim 36, wherein said gallium composition is a gallium-hydroxypyrone complex.

39. The composition of claim 36, wherein the nucleoside inhibitor is one or more of the compounds selected from the group of dideoxyinosine, dideoxycytidine and 5-azidothymidine.

40. A kit comprising, in suitable container means:

(a) a gallium composition; and

(b) a nucleoside reverse transcriptase inhibitor.

APPENDIX 2 -- EXHIBITS